

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
22 July 2004 (22.07.2004)

PCT

(10) International Publication Number  
**WO 2004/060403 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 47/48,**  
A61P 25/00

(74) Agent: **OGILVY RENAULT**; Suite 1600, 1981 McGill  
College Avenue, H3A 2Y3 Montréal, Québec, CA (CA).

(21) International Application Number:  
PCT/CA2004/000011

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 5 January 2004 (05.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/437,986 6 January 2003 (06.01.2003) US

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **TRANS-FERT PLUS** [CA/CA]; 550 Sherbrooke West, Suite 100, H3A 1B9 Montréal, Québec (CA).

(72) Inventors; and

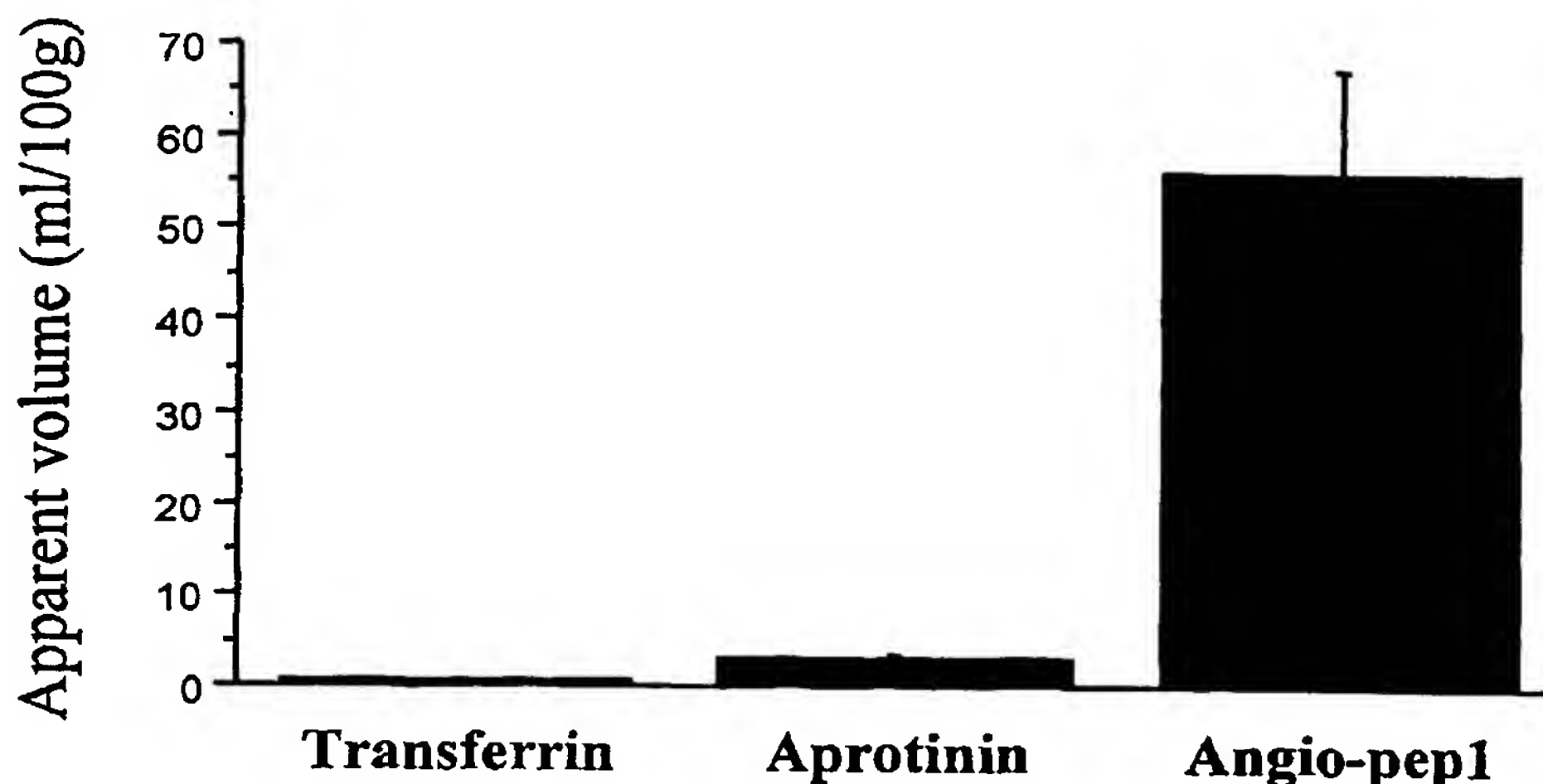
(75) Inventors/Applicants (*for US only*): **BÉLIVEAU, Richard** [CA/CA]; 266 Wilson, H3E 1L8 Montréal, Québec, CA (CA). **DEMEULE, Michel** [CA/CA]; 3557 Archambault, J4M 2W8 Longueuil, Québec, CA (CA).

Published:

— with international search report

[Continued on next page]

(54) Title: **APROTININ AND ANGLOS AS CARRIERS ACROSS THE BLOOD-BRAIN BARRIER**



(57) Abstract: The present invention relates to improvements in the field of drug delivery. More particularly, the invention relates to a non-invasive and flexible method and carrier for transporting a compound or drug across the blood-brain barrier of an individual. In particular the present invention relates to a carrier for transporting an agent attached thereto across a blood-brain barrier, wherein the carrier is able to cross the blood-brain barrier after attachment to the agent and thereby transport the agent across the blood-brain barrier. The present invention relates to improvements in the field of drug delivery. More particularly, the invention relates to a non-invasive and flexible method and carrier for transporting a compound or drug across the blood-brain barrier of an individual. In particular the present invention relates to a carrier for transporting an agent attached thereto across a blood-brain barrier, wherein the carrier is able to cross the blood-brain barrier after attachment to the agent and thereby transport the agent across the blood-brain barrier.

WO 2004/060403 A3



— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(88) Date of publication of the international search report:  
18 November 2004

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA2004/000011

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/48 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DE 199 53 696 A (CHERKASKY ALEXANDER) 10 May 2001 (2001-05-10)</p> <p>column 1, lines 15-32; claim 3; figure 1 ----- -/--</p>	<p>1-4, 7-21, 24-38, 41-53, 56-67, 70-78, 80-102</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 May 2004

Date of mailing of the international search report

30. 09. 2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Gonzalez Ramon, N

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA2004/000011

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHIMURA T ET AL: "TRANSPORT MECHANISM OF A NEW BEHAVIORALLY HIGHLY POTENT ADRENOCORTICOTROPIC HORMONE (ACTH) ANALOG, EBIRATIDE, THROUGH THE BLOOD-BRAIN BARRIER" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AMERICAN SOCIETY FOR PHARMACOLOGY AND, US, vol. 258, no. 2, 1991, pages 459-465, XP008030272 ISSN: 0022-3565 abstract; figure 1	1,2,4, 7-19,21, 24-36, 38, 41-51, 53, 56-65, 67, 70-77, 80-102
Y	----- DEMEULE M ET AL: "HIGH TRANSCYTOSIS OF MELANOTRANSFERRIN (P97) ACROSS THE BLOOD-BRAIN BARRIER" JOURNAL OF NEUROCHEMISTRY, NEW YORK, NY, US, vol. 83, no. 4, November 2002 (2002-11), pages 924-933, XP001188983 ISSN: 0022-3042 see discussion abstract	1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102
Y	----- SEIDEL G ET AL: "EFFECTS OF TRASYLOL ON THE BLOOD-BRAIN BARRIER IN RATS" NAUNYN-SCHMIEDEBERG'S ARCHIVES OF PHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 284, no. 4, 1974, page R73, XP008030270 ISSN: 0028-1298 abstract	1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102
Y	----- MARTEL ET AL: "Transport of apolipoproteins E and J at the blood - brain barrier. Relevance to Alzheimer's disease" STP PHARMA SCIENCES, PARIS, FR, vol. 7, no. 1, 1997, pages 28-36, XP002090769 ISSN: 1157-1489 abstract	1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102
P,X	----- WO 03/009815 A (KENNARD MALCOLM L ;YANG JOSEPH (CA); DEMEULE MICHEL (CA); BELIVEAU) 6 February 2003 (2003-02-06)  page 4; figure 17 page 37, line 8; claims 8,25 -----	1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102

-/--

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CA2004/000011

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 02/33090 A (PROCYON BIOPHARMA INC) 25 April 2002 (2002-04-25)</p> <p>page 1, lines 42,43; claims 12,22,36,46,52,58,75,82,88; example 18</p>	<p>1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102</p>
A	<p>-----</p> <p>GUILLOT F L ET AL: "ANGIOTENSIN PEPTIDE REGULATION OF BOVINE BRAIN MICROVESSEL ENDOTHELIAL CELL MONOLAYER PERMEABILITY" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, NEW YORK, NY, US, vol. 18, no. 2, 1991, pages 212-218, XP008030278 ISSN: 0160-2446 abstract page 217, column 2</p>	<p>1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102</p>
P,Y	<p>-----</p> <p>KOBAYASHI H ET AL: "THE PROTEASE INHIBITOR BIKUNIN, A NOVEL ANTI-METASTATIC AGENT" BIOLOGICAL CHEMISTRY, XX, XX, vol. 384, no. 5, 1 May 2003 (2003-05-01), pages 749-754, XP008030275 ISSN: 1431-6730 abstract; figure 2</p> <p>-----</p>	<p>1-5, 7-22, 24-39, 41-54, 56-68, 70-78, 80-102</p>

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA2004/000011

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-4, 7-21, 24-38, 41-53, 56-67, 70-78, 80-102 (all partially), 5, 22, 39  
54, 68

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 5, 22, 39, 54, 68 complete; 1-4, 7-21, 24-38, 41-53, 56-67, 70-78, 80-102 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is anticancer agent paclitaxel. Conjugate comprising the carrier and paclitaxel, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity).

---

2. claims: 1-4, 6-21, 23-38, 40-53, 55-67, 69-79, 80-102 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is a green fluorescent protein, a histag protein, and beta galactosidase. Conjugate comprising the carrier and the protein agent, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity)

---

3. claims: 1-4, 6-21, 23-38, 40-53, 55-67, 69-79, 80-102 partially

Carrier for transporting an agent attached thereto across the blood brain barrier wherein the agent is a green fluorescent protein, a histag protein, and beta galactosidase. Conjugate comprising the carrier and the protein agent, pharmaceutical composition and use of the same for neurological disease (brain tumour, brain metastasis, schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke and obesity)

---

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA2004/000011

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
DE 19953696	A		10-05-2001	DE	19953696	A1	10-05-2001
-----							
WO 03009815	A		06-02-2003	CA	2450073	A1	06-02-2003
				WO	03009815	A2	06-02-2003
				US	2003129186	A1	10-07-2003
-----							
WO 0233090	A		25-04-2002	CA	2321256	A1	16-04-2002
				CA	2355334	A1	16-04-2002
				AU	1369102	A	29-04-2002
				WO	0233090	A2	25-04-2002
				CA	2359650	A1	16-04-2002
				EP	1326981	A2	16-07-2003
				JP	2004510833	T	08-04-2004
				US	2003170220	A1	11-09-2003
-----							